REMARKS

Reconsideration is respectfully requested in view of the foregoing amendments and the remarks which follow.

Claims 1, 2, 10-24 have been amended. Claims 3-9, inclusive have been cancelled. Claims 31-37 have been added. Accordingly, the claims presently pending in the application are 1, 2, 10-24, and 31-37.

With respect to the objections in the specification, the term "~~even~~" at page 1, line 13, has been replaced with "only". In the specification, the term "~~exitocin~~" has been replaced with the term "oxytocin".

In view of the foregoing amendments, the objection has been overcome, and its withdrawal is respectfully solicited.

Claims 1-24 stand rejected under 35 U.S.C. §112, paragraphs 1 and 2. These rejections are respectfully traversed.

Each of the amended claims 1, 2, and 10-24 presented herewith has been amended to clarify that the pharmaceutical composition claimed is a *stable* composition which means that the pharmaceutical composition exhibits an extended shelf life. Support for such amendment can be found throughout the Application, for example on page 1, line 9, and on page 3, lines 9-13.

Further, each of the amended claims 1, 2, and 10-24 has also been amended to specify that the claimed compositions contain peptides which are selected from the group consisting of derivatives and analogues of *oxytocin* and *vasopressin* and their salts. Support for such amendment can be found in now cancelled claim 9.

Further, each of the amended claims 1, 2 and 10-24 have also been amended to specify that the claimed compositions contain a buffer.

Further, claim 1, and the claims dependent thereon, have been amended to specify that the claimed compositions are free from adsorption inhibitors and antioxidants and antimicrobial additives.

Applicants respectfully submit that in view of the amendment in each of the claims, of the former term "small or medium sized peptide" by the Markush group consisting of *oxytocin and vasopressin and their pharmaceutically acceptable analogues or derivatives*, the scope has been considerably reduced. With such restriction of the contemplated active principles to a circumscribed class of compounds of which the specific substance tested (namely desmopressin acetate) is a representative example, a sound extrapolation from the example given to the further claimed elements is justified from a scientific standpoint on the basis of the high homology in chemical structure and in physiological potency of the claimed compounds. A reasonable expectation of success is therefore provided for one of ordinary skill in the art.

Further restriction of the claimed subject-matter would, therefore, not be justified to one of ordinary skill in the art who is well aware of the structure/function analogies existing within a defined class of active principles. Applicant therefore submits that in view of the foregoing amendments the rejection has been overcome and a commensurate scope of the claims is established.

Deletion of the term "small or medium sized peptide" is also believed to overcome the indefiniteness objection raised with respect to claim 1.

Likewise, in amended claim 1, the term "preservatives" has been removed. Claim 1 now recites specifically the terms "antioxidants" and "antimicrobial agents", as specifically recommended in the Office Action.

As to the term "adsorption inhibitors", which is the third entity into which the earlier, more general term "preservatives" has now been broken down, a more exhaustive explanation arises from the passage in the specification discussing the prior art (in particular the paragraph bridging pages 1 and 2) and in turn from the literature cited therein. In particular, the Martindale Reference quoted at page 2, line 1 of the Application points out at page 736, second column, in the section dealing with interactions that: "*Like some other peptide drugs, calcitonin may be adsorbed onto the plastic of intravenous giving sets; it has been suggested that solutions for intravenous infusions should contain some protein to prevent the sorption and consequent loss of potency.*"

Further, with respect to insulin, the specification states, at page 2, lines 2-6 that Petty and Cunningham have reported in *Anaesthesiology* (see pages 403 and 404 of the article cited, in particular the sections "Prevention of Adsorption by Albumin and Plasma" and "Discussion") that: "*The addition of human serum albumin and Plasmanate was effective in decreasing the amount of insulin loss.*" Moreover, Harris *et al.* state in their example 5 that benzalkonium chloride and clorobutanol may work successfully as adsorption inhibitors, at least in the short-time testing (24h).

Thus, the specification of the Application points to a variety of well-known and specific examples of "adsorbtion inhibitors" recommended already in the prior art for the formulation of peptide drugs in low concentrated solutions. It is therefore submitted that the term "adsorbtion inhibitors" is adequately explained to one of ordinary skill in the art.

Since the transitional phrase in claim 2 is "*consisting of*", the presence of any further additive in addition to the ones specifically listed is excluded.

Claims 3 and 4 have been cancelled.

As to the dependency of claims 11 and 12, the Examiner's remark is correct in that a typographical error arose (namely "mercaptopropanyl" should be replaced by mercaptopropanoyl). With such correction, the dependency of claims 11-12 is correct.

Turning now to claims 19-24, it is stated that the osmolarity of human plasma (physiologic value) normally lies between 270 and 310 milliosmoles/l. It is well known in the art to impart such physiological value to pharmaceutical compositions, such as to increase their compatibility with human tissues and body fluids and such as to avoid pain upon administration. In this context, the preferred agent for controlling osmolarity is sodium chloride which, depending on the salt load already present, can be added in appropriate amounts, such as to arrive at the physiologic values. E.g. it is well-known that, if no salt load at all is present, i.e. if the osmolarity of pure water is to be controlled, a solution of 0.9% sodium chloride, the so-called "physiological" saline must be prepared.

The references already cited by the Examiner confirm such practice and they also show that the determination of the necessary amounts is merely a routine step for the skilled artisan. See e.g. Harris et al. (column 3, lines 9-12 and 21-23) showing that such practice is known and customary. See also the specific example provided by Florin-Robertsson in column 9, lines 6-8 where a specific sodium chloride addition has been calculated.

Hence it is believed that amended claims 19-24 are allowable.

Applicants respectfully submit that in view of the amendments made under §112, the rejections have been oercome and should, accordingly, be withdrawn.

Claims 1-17 stand rejected under §102(b) as anticipated by Harris et al., U.S. 5,482,931. In addition, claims 1-10, 12-13 and 15-18 stand rejected under §102(b) as anticipated by Begsston, U.S. 5,763,398. Further claims 1-10 and 12-13 stand rejected

under §102(b) as anticipated by Krupin et al., U.S. 4,853,375. The Examiner has also rejected claims 1-11 and 13 under §102(b) as anticipated by Fredholt et al., (Int. J. Pharm. 1999). The Examiner has also rejected claims 1-8, 13 and 16-18 under §102(b) as anticipated by Florin-Robertsson et al., U.S. 5,783,559. These rejections are all respectfully traversed.

Claim 1, as amended, recites in pertinent part: "A **stable pharmaceutical composition** containing a therapeutically effective amount of a peptide ... in aqueous solution, wherein it is **free from adsorption inhibitors preventing adsorption of the active principle onto container walls and free from antioxidants and antimicrobial additives**". (Emphasis added)

Likewise, amended claim 2 recites in pertinent part: "A **stable pharmaceutical composition** consisting of a therapeutically effective amount of a peptide ... in aqueous solution." (Emphasis added)

As defined in the instant specification, "the pharmaceutical compositions of the invention, unlike test compositions prepared for clinical trials or for short-term potency investigations on laboratory scale, are intended as marketable, ready-to-use products exhibiting an extended shelf-life," see page 3, lines 9-13 spelling out this definition. As shown in examples 3-5 of the instant application (see pages 6-8), the pharmaceutical compositions of the present invention did not undergo any significant titre loss, neither in the short term experiments (4 days) nor in the long term testing (up to 18 months).

Hence, Applicant has demonstrated that both pharmaceutical compositions of claims 1 and 2 are stable for extended periods, though none of them contains adsorbtion inhibitors, antioxidants or antimicrobial agents.

In contrast thereto, as will be shown below, the prior art cited fails to disclose a *stable* pharmaceutical composition *free* from adsorption inhibitors and *free* from antioxidants and antimicrobial additives.

In fact, Harris teaches that a stable aqueous composition of the type at issue necessarily requires the presence of a quarternary amine preservative or disinfectant. Thus, the composition disclosed by Harris is distinguishable from the one claimed by the Applicant.

As to the further peptide solution disclosed by Harris in column 5, lines 54-56, it should be noted that the solution is clearly not a *pharmaceutical composition* in the sense of Applicant's claim, but, instead, a laboratory sample prepared for the comparative testing carried out by Harris. In particular, as Harris himself reports, the sample solution prepared by Harris appears to have given unsatisfactory results, namely, the solution degraded within a time span much shorter than any technically meaningful "shelf-life" would be. Therefore, one skilled in the art would have never contemplated putting such a peptide solution on the market as a pharmaceutical product. It would therefore go completely against the teaching of Harris, and more particularly against the specific context in which the quoted passage is embedded, if the comparative embodiment of example 5 was taken as a disclosure of a successful preparation of a *stable* pharmaceutical product. Rather, the contrary is true. Accordingly, Harris cannot be said, in any manner, to anticipate Applicant's invention.

Also Bengtsson, who has investigated the influence of specific doses of active principle on the plasma level obtained in a patient, fails to disclose -even accidentally- a *stable* pharmaceutical composition free from adsorption inhibitors and free from antioxidants and antimicrobial additives. In particular, Bengtsson is completely silent

about any behaviour over time whatsoever of the single dose compositions disclosed at column 3, lines 3-11. Accordingly, the quoted passage in column 3, would be reasonably understood by one skilled in the art in a way that additives heretofore deemed critical in the preparation of pharmaceutical compositions of peptides (and considerable evidence for the active existence of such prejudice in the art is on file) would be stated by Bengtsson here as being unexpectedly totally optional or superfluous. Rather, it becomes clear that Bengtsson's assertion arises from the use of a legalistic language and not from a scientific investigation of *stability*. Accordingly, Bengtsson does not anticipate Applicant's invention.

Also Krupin fails to disclose Applicant's invention. This is because the solution described in the passage according to column 3, lines 9-21 of Krupin, is not stated to be a *stable pharmaceutical solution*. Even less is there any disclosure of the solution's *long-term behaviour*. Neither are these important features of Applicant's invention even implicitly at issue in Krupin, since it arises from the context that Krupin's solution is prepared –most probably on the spot- to induce an intraocular pressure rise within an animal model intended in its turn to study the efficacy of tetracyclines in the therapy of glaucoma. It therefore appears that the solution used by Krupin is intended exclusively as an experimental tool for the induction (and not for the healing) of a disease. Already on these grounds, it cannot be regarded even as a *pharmaceutical product*. Therefore, the skilled investigator would understand that Krupin's solution –at best- as a "test composition prepared for (clinical) trials or for short term potency investigations on laboratory scale" (see page 3, lines 10-11 of the instant Application), i.e. a type of composition explicitly excluded from Applicant's claims. Hence, the Krupin reference does not anticipate Applicant's claims.

Also Fredholt does not disclose Applicant's invention. This is because Fredholt's article is concerned with the study of the chymotrypsin-mediated *in vitro* degradation of desmopressin and with the ability of cyclodextrins to inhibit such degradation, which occurs normally in the patient's gut if the desmopressin is administered perorally, to the detriment of the desmopressin's bioavailability. Since chymotrypsin is obviously normally not a component of desmopressin compositions, the particular *in vitro* conditions adopted by Fredholt are clearly not intended for the manufacture of pharmaceutical products. This applies also to the chymoptrypsin-free test solution reported in table 2 of Fredholt which is intended exclusively as a comparative standard simulating the background pH conditions occurring in the duodenum (see page 226, column 1, last-but-fourth line). Indeed, such control solution was not subjected to any extended shelf life testing whatsoever. Hence, the chymoptrypsin-free solution of table 2 is one "for short term investigations on laboratory scale" (see page 3, lines 10-11 of the instant Application) as specifically excluded by the claim.

Neither does Florin-Robertsson disclose Applicant's invention as presently claimed. Indeed, Florin-Robertsson has investigated compositions containing Insulin-like Human Growth Factor and not compositions containing oxytocin or vasopressin. Just on this basis alone, Applicant's claims distinguish over Florin-Robertsson.

For at least the reasons outlined above, Applicant respectfully submits that each of the independent claims 1 and 2 is novel over the prior art cited. All of the dependent claims are likewise deemed novel by the virtue of their dependency from claims 1 and 2. Hence, the Applicant respectfully requests reconsideration and withdrawal of the §102(b) rejections.

Claims 1-24 stand rejected under §103(a) over the combination of Harris et al., in view of Florin-Robertson et al., and Fredholt et al. Claims 1-24 also stand rejected under §103(a) over the combination of Begsston in view of Harris et al., in view of Fredholt et al., and Florin-Robertsson et al. Claims 1-24 also stand rejected under §103(a) over the combination of Florin-Robertsson et al., in view of Harris et al., and Fredholt et al. These rejections are respectfully traversed.

As to the combination of Harris with Florin-Robertsson and Fredholt, it has already been pointed out previously that Harris discloses, in the first place, that the inclusion of an adsorption inhibitor is absolutely necessary to arrive at stable pharmaceutical solutions of oxypressin and vasopressin. Moreover, since the necessity of peptide solutions to be formulated together with specific additives was well-known in the art (as confirmed e.g. through the respective remark made in Florin-Robertsson, column 2, lines 10-14), it is already doubtful, if the person of ordinary skill in the art would have contemplated the preservative-free solution of column 3, lines 56-57 of Harris as an adequate starting point for the development of a pharmaceutical composition. In other words, the embodiment which has been explicitly discredited by Harris could hardly be regarded as the first step of an "obvious" strategy, since clearly going against the gist of Harris' overall teaching.

However, even if the preservative-free solution of Harris was excised from its context (and, once again, it is not at all clear how this could be reasonably done without the hindsight knowledge derived solely from Applicant's invention) then it would not at all have been straightforward for the skilled artisan, pursuing the aim of developing a pharmaceutical product displaying an extended shelf-life, to modify Harris' preservative-free test solution in the manner suggested in Florin-Robertsson. This is because the Florin-Robertsson reference (whose authors, unlike the present inventors, prepare injectables)

clearly concerns an active principle which is different and distinguishable from the one of Applicant's invention. It is submitted that such difference is more than merely formal in nature, in that there can be no doubt that the amino acid sequence and the molecular weight of insulin-like growth factor and of the claimed protein are *markedly* distinct. Moreover, it has to be remembered, once again, that for the skilled artisan, it would be not at all usual or normal to construe documents *against* specific warnings contained in the documents, see column 2, lines 56-66, stating:

"Proteins are different with regard to physiological properties. When preparing a pharmaceutical preparation which should be physiologically acceptable, and stable for a long time, consideration can not only be taken to the physiological properties of the protein but also other aspects must be considered such as the industrial manufacture, easy handling for the patient and safety for the patient. The results of these aspects are not predictable when testing different formulations and each protein has often a unique solution regarding stability."

Hence, from the disclosure in the Florin-Robertsson reference, it cannot be deduced in any manner that it would be somehow *straightforward* to obtain acceptable results, if the active principle was switched. Rather, the contrary is true.

Therefore, since both references, already on their own, teach away from Applicant's invention, one of ordinary skill in the art would never have been motivated to combine them, and even less, would he have been motivated to disregard Florin-Robertsson's teaching quoted above, namely, that the stabilization of protein solutions normally requires measures carefully tailored on demand.

The skilled artisan's reasonable understanding of th prior art, according to which no improvement could have been expected through the combination of Harris and Florin-Robertsson remains the same, even if Fredholt is taken into account.

As outlined above, the chymotrypsin-free solution disclosed in table 2 of Fredholt was prepared exclusively for comparative testing and *does not* constitute a pharmaceutical product. Furthermore, this specific solution would not have been considered by one skilled in the art as a reasonable or logical starting point in the design of a pharmaceutical product. Since quite clearly there is no reference whatsoever to any reasonable extended shelf-life testing, but, even more importantly, because the skilled artisan would normally not deduce from the data disclosed in table 2 of Fredholt, that the additives heretofore explicitly recommended for the pharmaceutical products in the prior art were not necessary.

Indeed, the chymotrypsin-free solution according to table 2 was prepared by Fredholt in order to obtain a reading of the putative desmopressin background decay within two days. However, degradation due to e.g. a possible solution-container interaction was not investigated at all by Fredholt in an isolated manner. That is to say, for the experimental design as adopted by Fredholt –namely in view of the aim of carrying out an *in vitro* simulation of a gut environment- any solution-container interaction was obviously *an unwanted parameter* whose influence had to be excised from the measurements. Thus, in view of the specific target pursued through Fredholt's experiment, it would go counter to and against a skilled artisan's understanding of the disclosure, if one assumed now that Fredholt, in loading the chymotrypsin blanks on the chromatographic equipment for analysis, would not have carried out a meticulous and repeated rinsing of the containers with fresh buffer, as is customary practice in analytical determinations.

Hence, in the absence of any declared intention of Fredholt to pinpoint the container-solution interactions (and indeed, nowhere in th reference can there be found any allusion whatsoever to the container as such and to the material it consists of), it cannot be reasonably assumed that Fredholt proceeded –silently(!)- against the normal analytical practice of quantitative transfer of sample solutions to the analyzer, a practice which excises the influence of container-solution interactions.

Rather, if container-solution interactions, *had been* an issue to Fredholt, she *would* have reported about the container material, and she *would* have described how the experimental layout or design was *explicitly modified* with respect to the usual practice, namely to specifically isolate and highlight the influence of such interactions.

Therefore, if Fredholt states on page 226 (see column 1, next-to-last paragraph) that "no degradation was found after incubation of desmopressin in 0.1 M phosphate buffer pH 7.40 for 2 days" she reports data which are valid, in reality, for the bulk of the blank solution. On these grounds, the skilled artisan, who interprets the results in the light of the experimental protocol followed, would never take this statement as a declaration of the absence of surface absorption phenomena.

Therefore, the article of Fredholt does not at all disclose or even suggest, to one of ordinary skill - neither explicitly nor impliedly - that the totally different problem of dispensing pharmaceutical peptide solutions, all-at-once, from commercial storage containers has been solved or could have been solved by formulating pharmaceutical products in the manner in which Fredholt prepares her analytical test solutions for the background calibration in the measurement of desmopressin digestion by chymoptrypsin.

The foregoing is true for the combination of Bengtsson with Harris and with Fredholt and Florin-Robertsson.

As pointed out above, Bengtsson has not carried out any stability testing of the solutions claimed. Therefore, it is clear to the skilled man that Bengtsson's claim 1 as well as the explicative passage in column 3, lines 3-5 (..."may contain"...) are a semantic definition of the requested scope of *legal* protection, rather than an active statement or an indication that preservatives which had been deemed critical in the prior art, could have been omitted. At least, in the absence of any experimentation in that respect, such an interpretation of the Bengtsson reference would not be adopted by the skilled man, in particular in view of the prejudice in this respect, known in the art, and literally spelled out in Harris (claim 1). In other words, in particular the teaching of Harris would prevent the skilled man from interpreting the passage in column 3, lines 3-5 of Bengtsson across its semantic breadth. Neither the Florin-Robertsson reference (which concerns a different active principle) nor the Fredholt article (which is not concerned with pharmaceutical solutions), if considered additionally in the evaluation of the first two references, would provide a pointer or guidepost to Applicant's invention.

As far as a combination of Florin-Robertsson with Harris and Fredholt is concerned, Applicants have already outlined above that Florin-Robertsson not only does not provide for the claimed results, but also teaches away from the extrapolation of its content to different active principles. Therefore, nothing in Florin-Robertsson suggests that, contrary to what is stated explicitly in Harris (claim1), the additive load in pharmaceutical desmopressin solutions could be further reduced. On the other hand, Fredholt cannot be reasonably taken (in spite of her statement at page 226, (next to last paragraph) as defeating the teachings of Florin-Robertsson and Harris, since the skilled artisan, upon examining the experimental work reported by Fredholt, would learn that surface phenomena were not subject to study. Hence, Fredholt's article would not work as

a pointer or provide guidance to substantially change the composition of known commercial desmopressin or vasopressin solutions, *contrary* to what is stated in Florin-Robertsson and Harris.

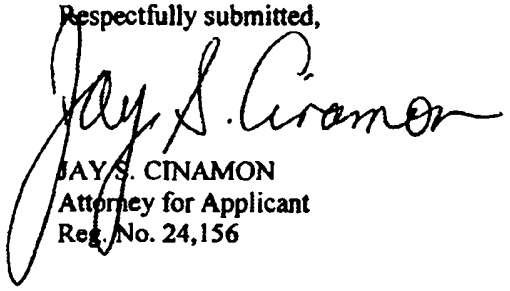
All in all, since the skilled artisan, unless he had the benefit of hindsight knowledge obtained from the claimed invention, would normally not interpret specific passages of a document against the overall gist of the document, and neither would he construe specific passages unreasonably, i.e., outside the specific context in which they were made, it is clearly apparent that the invention was unobvious to one of ordinary skill in the art in the light of the references cited.

For at least the reasons outlined above, Applicants respectfully submit that the claims distinguish over the prior art cited. Withdrawal of the obviousness rejections is respectfully solicited since a *prima facie* case of obviousness has notbeen established.

The issuance of a Notice of Allowance is respectfully solicited.

Please charge any fees which are due and which have not been submitted herewith to our Deposit Account No. 01-0035.

Respectfully submitted,



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